Ambulatory Norepinephrine Treatment of Severe Autonomic Orthostatic Hypotension

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OBJECTIVES This study was designed to establish a patient-controlled, ambulatory norepinephrine treatment of refractory orthostatic hypotension due to primary autonomic failure.

BACKGROUND Autonomic dysfunction leads to disabling postural hypotension. Particularly in primary autonomic dysfunction, repeated syncope and immobilization can be the result. Medical treatment of orthostatic hypotension often fails in advanced cases.

METHODS Ambulatory, patient-controlled norepinephrine therapy was initiated in six patients with orthostatic hypotension due to primary autonomic failure that had been refractory to conventional treatment. Before this therapy, three patients were bedridden; one was immobilized in a wheelchair. All had recurrent syncope and tolerated upright tilt-table testing for less than 15 min despite extensive medical treatment. For ambulatory treatment, a port-a-cath system was implanted and, using a CADD ambulatory infusion pump, norepinephrine was infused in individually adjusted dosages.

RESULTS Norepinephrine infusion therapy enabled all patients to sit, stay and walk around for more than 45 min. One patient died after a five-year treatment period, another after nine months because of nonhemorrhagic brain stem infarctions, both in the absence of norepinephrine treatment. The remaining four patients are still mobile after a period of 19, 10, 9 and 7 months, respectively. None of them has suffered complications due to arterial hypo- or hypertension, and there has been no infection of the infusion system.

CONCLUSIONS In these selected patients with refractory orthostatic hypotension due to primary autonomic dysfunction, ambulatory norepinephrine infusion therapy has proved to be a promising new therapeutic option. Further long-term studies including more patients are necessary to assess additional indications, reliability and safety of this new method. (J Am Coll Cardiol 2001;37: 219–23) © 2001 by the American College of Cardiology
static hypotension and the associated symptoms in these patients (Table 1); three of them were still bedridden, and one patient with Shy-Drager syndrome was still confined to his wheelchair. Therefore, we tested the effects of intravenous infusion of norepinephrine. We administered norepinephrine in increasing individual dosages (5 to 20 ng/kg body weight/min) using a temporary intravenous indwelling catheter and an infusion pump (Original Perfusor Braun, B. Braun Melsungen, Melsungen, Germany). Blood pressure was continuously monitored (Dinamap). The administration of norepinephrine was started in the supine position. After systolic BP had risen about 20 to 30 mm Hg, the patients were allowed to sit up. Then the patients were mobilized, and norepinephrine dosages were adjusted several times during standing and stopped before sitting or lying down. A bolus application on demand was necessary to maintain adequate BP while changing from supine to sitting or from sitting to an upright position. Additionally, it was necessary to work out two different dosages, one for sitting and a higher one for standing position in some patients. Success of the temporary norepinephrine infusion was the requirement for the implantation of a permanent intravenous-infusion system.

**Permanent norepinephrine infusion.** After elucidation about potential hazards of a continuous and self-controlled norepinephrine therapy (e.g., infections, embolization, hypertension and stroke), written informed consent was obtained. A port-a-cath (SIMS Deltec Inc., St. Paul, Minnesota) system was implanted, and every patient was taught to handle an ambulatory infusion pump (CADD, SIMS Deltec Inc., St. Paul, Minnesota). In cooperation with the patients and their relatives and during continuous noninvasive BP monitoring, individual dosages for sitting, standing and walking were established. Individual programming of the infusion pump was necessary to find an optimal treatment regimen. In general, mobilization and ambulation of the patients with Bradbury-Eggleston syndrome was much easier than it was for the patients with accompanying Parkinson symptoms (Shy-Drager syndrome).

Before entering an upright or sitting position, the patient had to switch on the system to start the continuous administration of norepinephrine. Additional bolus on demand were given to fill the port-a-cath system and to change from a supine to a sitting or upright position. The pump was switched off or adjusted to a lower infusion rate immediately before sitting or lying down to avoid episodes of severe hypertension in supine or sitting positions.

**Follow-up.** After discharge from the hospital, follow-up visits at least every three months were arranged in our program. From the data obtained after discharge, the long-term effectiveness of the treatment could be evaluated. The patients were questioned about general side effects of therapy, e.g., infections or symptoms due to circulatory problems. The limited walking distance during norepinephrine treatment in patients with Shy-Drager syndrome is due to impaired coordination, physical strength and coordination problems due to parkinsonism.

### Table 1. Clinical Characteristics of Patients Treated With Norepinephrine

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Syndrome</th>
<th>Tilt tolerance, 60° head-up tilt-test (min)</th>
<th>Walking distance (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>Male</td>
<td>Bradbury-Eggleston</td>
<td>&lt; 10</td>
<td>Unlimited</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>Female</td>
<td>Shy-Drager</td>
<td>&gt; 10</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>Female</td>
<td>Shy-Drager</td>
<td>&gt; 10</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>Male</td>
<td>Shy-Drager</td>
<td>&gt; 10</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>Female</td>
<td>Shy-Drager</td>
<td>&gt; 10</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>Male</td>
<td>Shy-Drager</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
</tr>
</tbody>
</table>

Table 1. Tilt tolerance describes the maximum tolerated time of the 60° head-up tilt-table test before the onset of presyncope or syncope. The limited walking distance during norepinephrine treatment in patients with Shy-Drager syndrome is due to impaired coordination, physical strength and coordination problems due to parkinsonism.
outpatient clinic. During these visits, the history and a full physical examination were obtained, and repeated BP measurements, including 24-h ambulatory measurements, were taken to determine whether the infusion dosage was still optimally adjusted. Special attention was taken to maintain the integrity of the infusion system and to watch for signs of infection. The family physician, a surgeon or an anesthesiologist in cooperation with a local pharmacy replaced drug cassettes, port-needles and infusion systems.

**Parameters of successful treatment.** Success of the therapy was assessed as degree of mobilization, including determination of unimpaired walking distance, 60° upright tilt-table tests and 24-h ambulatory BP monitoring.

**Ethics.** Written informed consent was obtained. The local ethics committee approved the study protocol, and all investigations were conducted according to Good Clinical Practice guidelines.

**RESULTS**

**Symptoms and syncope.** Symptoms of orthostatic hypotension, like dizziness, blurred vision, dyspnea and nausea, were noticeably improved in all patients and limited to errors in operating the infusion pump. These consisted of starting the infusion late on the one hand or unnecessary bolus applications with consecutive short hypertensive episodes on the other hand. No syncope occurred during appropriate norepinephrine infusion.

**Walking distance.** During continuous norepinephrine infusion, all patients were mobilized and enabled to walk around unaided. None of the patients was bedridden or confined to a wheelchair anymore. The walking distance in patients with Bradbury-Eggleston syndrome was unlimited, whereas it was finite in patients with Shy-Drager syndrome. Nevertheless, the latter increased their distance about 4 to 25-fold compared with conventional medical treatment.

**Tilt-table testing.** Tilt-table results during patient-controlled norepinephrine infusion improved markedly compared with the initial testing or combined nonpharmacological and pharmacological (conventional) treatment (Table 1). As an example of successful norepinephrine therapy, Figure 1 shows the tilt-table results of a patient with Shy-Drager syndrome (Patient 4). During conventional treatment, orthostatic hypotension with syncope occurred after 10 min at a mean arterial BP of 50 mm Hg, whereas norepinephrine infusion enabled the patient to tolerate 45 min of tilt-table testing without symptoms. In both cases, heart rate did not change notably.

**Ambulatory BP measurements.** Intermittent and continuous 24-h BP measurements showed markedly reduced episodes of orthostatic hypotension during norepinephrine infusion therapy. Figure 2 shows the example of a patient with Shy-Drager syndrome (Patient 4) in whom recurrent episodes of orthostatic hypotension were successfully treated with the new therapy. In general, supine hypertensive episodes were markedly decreased compared with conventional treatment, whereas short episodes of hypertension occurred during a delayed turn off while sitting or lying down or if inappropriate bolus applications were given.

**Long-term follow-up.** Ambulatory norepinephrine therapy was successful initially in all six patients in the program. The longest therapy period was five years in a female patient with Shy-Drager syndrome (Patient 6). This patient died at age 75 years because of a nonhemorrhagic brain stem infarction that occurred one morning while she tried to get up without starting the infusion pump.

A second non-hemorrhagic stroke was responsible for the death of a 72-year-old patient with Shy-Drager syndrome (Patient 5). In this case, ambulatory infusion therapy was stopped six months earlier. Increasing compliance and coordination problems had led the family physician to stop the norepinephrine treatment. Although conventional therapy had been reintroduced, the patient was confined to his wheelchair again.

The other four patients are still being treated successfully and have been mobile for a period of 19, 10, 9 and 7 months, respectively. Infections or embolization have not occurred in any case; hospitalization has been necessary in only one patient (Patient 1) at one-year follow-up.

**DISCUSSION**

Autonomic orthostatic hypotension is a rare but severely disabling condition. Impaired autonomic reflexes with inadequate rise of plasma catecholamine levels and an almost fixed heart rate lead to a decrease in BP because of the deficient vasoconstrictor tone and the lack of increase in heart rate (16,17). The upright position is associated with symptoms like blurred vision, light-headedness, dizziness, head and neck discomfort, presyncope or even syncope.

**Conventional treatment.** The conventional approach in treating patients with autonomic orthostatic hypotension consists of a combination of nonpharmacological and pharmacological regimens of increasing intensity (5,9–12,14,15,18,19). Regardless of optimal nonpharmacological or pharmacological treatment, the autonomic insufficiency...
can lead to immobilization and confinement to bed in advanced cases. Another disadvantage of the conventional medical treatment is the development or the worsening of hypertension in patients who remain in the supine position (20).

**Norepinephrine infusion.** Polinsky et al. (3) first used a temporary norepinephrine infusion to overcome orthostatic hypotension during tilt-table testing in two patients with Shy-Drager syndrome. The aim of the current study was to establish an ambulatory and long-term treatment of orthostatic hypotension in cases of severe autonomic failure. We tested the effects of a patient-controlled, ambulatory norepinephrine infusion therapy on BP in supine, sitting and upright positions. In all patients, norepinephrine infusion prevented symptomatic orthostatic hypotension; mobilization was possible in all cases, and some patients were able to walk for the first time in months.

**Infusion system.** The port-a-cath system is a widely used system for intermittent application of different chemotherapeutic agents, mostly in patients with cancer or AIDS. In patients with an impaired immune system, the overall complication rate is 13% to 19%; infections occur in 2% to 5% and occlusions in 3% to 6.5% of all cases (21,22). We have not observed complications related to the implantable venous catheter system.

**Advantages and limitations.** The major advantages of the new therapeutic tool were the ability to mobilize patients previously confined to bed and to avoid syncope. The efficacy has been well-documented in symptom-free head-up tilt-table tests and in increased walking distance. Treatment on demand meant that pre-existing hypertension present in the supine position was not aggravated. The requirement of compliant patients, who can handle the system, is a possible limitation of this new therapeutic approach. Mobilization proved to be much easier in patients without accompanying Parkinson-like neurological symptoms (Bradbury-Eggleston syndrome) than it was for patients with Shy-Drager syndrome. Even this therapeutic approach will not prevent serious complications of the underlying disease in all instances. But although difficulties arose in some cases, an improved quality of life was conveyed to patients with both syndromes.

**Conclusions.** In selected patients with severe and refractory orthostatic hypotension due to autonomic failure, ambulatory and patient-controlled norepinephrine treatment seems to be a promising long-term therapy in compliant patients. However, further studies enrolling larger patient numbers are necessary to establish the role of ambulatory norepinephrine infusion in the treatment of autonomic orthostatic hypotension and to assess additional indications, reliability and safety of this new method.

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REFERENCES


